

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Infukoll[®] 6 % solution for infusion, bag

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1000 ml contains:

Poly (O-2-hydroxyethyl)starch (Molar substitution (Average molecular weight:	0.45-0.55) 200 000 Da)	60.0	g
Sodium chloride		9.00	g
Na ⁺		154	mmol
Cl ⁻		154	mmol
Theoretical osmolarity		309	mosmol/l
pH		5.0-7.0	

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion

Clear, colourless, aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment and prevention of hypovolaemia and shock.
Normovolaemic haemodilution.

4.2 Posology and method of administration

HES must be administered intravenously.

Total dosage, duration and rate of infusion will depend upon the amount of blood lost and/or the haemodynamic status and general clinical condition of the patient. Dosage will need to be adjusted as necessary by monitoring the usual circulatory parameters e.g. blood pressure.

The risk of circulatory overload by too rapid rate of infusion or inappropriately large doses must be borne in mind.

Due to the risk for occurrence of an anaphylactic reaction, the first 10 ml - 20 ml of Infukoll[®] 6 % should be infused slowly and under careful observation of the patient.

Maximum infusion rate:

The maximum rate of infusion should be adjusted to the clinical situation.

Patients with acute haemorrhagic shock: Up to 20 ml/kg bodyweight/hour (equivalent to 0.33 ml/kg BW/min).

In life-threatening situations: 500 ml as a rapid infusion (under pressure). The rates of infusion selected for perioperative indications and for burns and septic shock patients will usually be lower.

Maximum daily dosage:

A maximum daily dosage of 2 g/kg bodyweight/day of hydroxyethyl starch (HES) should not be exceeded. This corresponds to 33 ml/kg bodyweight/day of the 6 % solution (approximately 2,500 ml/day in a person of 75 kg). Experience of treatment of more than 1-2 days is limited. In cases of longer treatment the daily doses have generally been lower. An increasing risk of undesirable effects with high cumulative doses (see section 4.8) should be considered.

Children:

There are no data concerning usage of Infukoll® 6 % in children.

Administration to children should only be managed after careful benefit/risk assessment.

Further information:

Patients with primarily interstitial fluid losses must firstly be treated with crystalloids. After infusion of HES controls of serum electrolytes and fluid balance are required. Electrolytes must be administered as required. In all patients adequate fluid supply is essential. Renal function must be monitored during treatment (control of serum creatinine). Because of the possibility of allergic (anaphylactic/anaphylactoid) reactions, appropriate monitoring of patients is necessary (see section 4.4).

4.3 Contraindications

- Known hypersensitivity to hydroxyethyl starch
- Hypervolaemia
- Hyper-hydration (e.g. water intoxication)
- Hyperchloraemia (or hypernatraemia)
- Congestive cardiac failure
- Pulmonary oedema
- Renal failure, with oliguria and anuria
- Cerebral haemorrhage
- Severe blood coagulation disorders
- Severe hepatic impairment

4.4 Special warnings and precautions for use

Particular caution should be exercised and the dosage adjusted as appropriate in patients who have impaired renal clearance since this is the principal way in which Infukoll® 6 % is eliminated. In these patients especially, adequate fluid supply is essential. Renal function, including serum creatinine, must be monitored both before and during treatment.

Monitoring of the serum electrolytes and fluid balance is necessary.

Circulatory overload: The possibility of circulatory overload should be considered. Caution should be exercised in patients at risk of pulmonary oedema and/or congestive cardiac failure; and severely impaired renal function.

Because of the possibility of allergic (anaphylactic/anaphylactoid) reactions, appropriate monitoring of patients is necessary (see section 4.4).

In case of an allergic reaction, the infusion must be stopped immediately and appropriate treatment given.

Like all colloidal plasma substitutes, Infukoll® 6 % produces coagulation factor dilution. In particular, there is a change in Factor VIII activity, which is, however, temporary and reversible, and, in the absence of other blood coagulation

disorders, has no clinical significance. Infukoll[®] 6 % should be used with caution in patients with preexisting blood coagulation disorders, impaired hepatic function or haemorrhagic diathesis.

Haematocrit may be decreased and plasma proteins diluted by infusion of large volumes of Infukoll[®] 6 %.

Administration of packed red cells, fresh frozen plasma, platelets or full blood should also be considered if excessive dilution occurs.

Samples for blood group determination must be obtained before HES administration because the product may interfere with the tests and cause false positive answers for irregular agglutinins.

Elevated serum alpha amylase concentrations about three times the upper limit of normal may be observed temporarily following administration of HES solutions which may interfere with the diagnosis of pancreatitis. This elevated alpha amylase activity is due to the formation of an enzyme-substrate complex of amylase and HES subject to slow renal elimination and therefore must not be considered diagnostic of impaired pancreatic function (see sections 4.8 and 5.2).

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of heparin or oral anticoagulants may increase coagulation time.

4.6 Pregnancy and lactation

For Infukoll[®] 6 % no clinical data on exposed pregnancies are available. No reproductive toxicological studies in animals with Infukoll[®] 6 % have been performed, but studies with similar hydroxyethyl starch products have caused vaginal bleeding and embryoletality during repeated treatment of test animals. Harmful embryo effects may occur with HES associated anaphylactic reactions in the pregnant mother. Infukoll[®] 6 % should only be used during pregnancy when the potential effects outweigh the potential risks to the embryo.

There is as yet no experience with usage of this product in nursing mothers.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Medical products containing hydroxyethyl starch may in rare cases cause anaphylactic reactions of varying degrees of severity.

In the event of an allergic reaction, the infusion must be stopped immediately and appropriate measures to manage the reaction in response to its intensity must be taken (see section 4.4).

Administration of hydroxyethyl starch may result in dose dependent coagulation disturbances. A transient fall in Factor VIII levels may be seen followed by a prolonged coagulation time. This lacks clinical relevance in the majority of patients. Haematocrit value may be decreased and plasma proteins diluted by infusion of large volumes of Infukoll[®] 6 % (see section 4.4).

The concentration of serum α -amylase may increase during the infusion of hydroxyethyl starch. This elevated α -amylase is due to the formation of an enzyme-substrate complex of amylase and hydroxyethyl starch subject to slow renal elimination and must not be considered diagnostic of pancreatitis.

Itching is a known adverse event after long-term administration of high doses of hydroxyethyl starch. This itching may not appear until weeks after the last infusion and may persist for months.

4.9 Overdose

The main risk of an acute overdose would be volume overload. In this case infusion must be stopped immediately and if necessary diuretics should be administered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Blood substitute and plasma proteins. ATC code: B 05 AA 07.

Infukoll[®] 6 % is a colloidal plasma volume substitute containing 6 % hydroxyethyl starch (HES) in isotonic saline (0.9 % sodium chloride). The average molecular weight (Mw) of the colloid is 200,000 Da and the molar substitution (MS) 0.45 - 0.55, meaning that HES on average contains approximately 5 hydroxyethyl groups per 10 glucose units.

Infukoll[®] 6 % is iso-oncotic, i.e., the increase in plasma volume is approximately 100% of the infused volume.

The duration of the plasma volume effect depends primarily on the level of molecular substitution and to a lesser extent on the average molecular weight. Intravascular hydrolysis of the hydroxyethyl starch polymers continually releases smaller molecules, which, in turn, are oncotically active before being eliminated via the kidneys.

Infusion of Infukoll[®] 6 % lowers haematocrit and plasma viscosity.

After infusion of Infukoll[®] 6 % to hypovolaemic patients the blood volume increasing effect is in general maintained for 3 to 6 hours.

5.2 Pharmacokinetic properties

Hydroxyethyl starch is a mixture of several different substances with different degree of substitution and molecular weight. The elimination depends on molecular weight and degree of substitution. Molecules smaller than the renal threshold (60 000 Da – 70 000 Da) are eliminated via glomerular filtration. Larger molecules are degraded by α -amylase and are thereafter eliminated renally. The rate of degradation decreases with increased degree of substitution. The initial half-life in serum is approximately 6 hours. Approximately 50 % of a given dose is excreted into urine within 24 hours.

5.3 Preclinical safety data

No toxicological animal studies have been conducted with Infukoll[®] 6 %. Publications of toxicological evaluations of animal studies conducted with repeated hypervolemic treatment with similar hydroxyethyl starch products have shown bleeding and histiocytosis (accumulation of foam-like histiocytes/macrophages) in several organs including gained weight of the liver, kidneys and the spleen. Infiltration of fat and vacuolation of organs and increasing plasma ASAT and ALAT have been reported. Possible explanations of some of these effects are blood dilution, increased circulatory load and uptake and accumulation of starch in phagocytosing cells.

Similar hydroxyethyl starch products have been reported to not be geno-toxic during standard testing. Repro-toxicological studies of similar hydroxyethyl starch products have not shown any signs of teratogenicity. However, vaginal bleeding and embryo-lethal effects have been observed after evaluation of repeated treatment of test animals.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections.

6.2 Incompatibilities

In the absence of incompatibility studies this medicinal product must not be mixed with other medicinal products.

6.3 Shelf Life

Bags 2 years

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

Infukoll[®] 6 % is available in the following containers and pack sizes:

Bags (plastic polypropylene) with stopper (chlorobutyl rubber) and outer bag (polypropylene) 10 x 500 ml

6.6 Instructions for use and handling

Use immediately after first opening and discard any unused product.

Use clear solutions from intact containers.

7 MARKETING AUTHORISATION HOLDER

Serumwerk Bernburg AG
Hallesche Landstrasse 105 b
06406 Bernburg
Germany

8 MARKETING AUTHORISATION NUMBER

PA 1136/1/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 June 2004

10 DATE OF REVISION OF THE TEXT